The Knee xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

The Knee

TNF-α concentrations in pre-operative synovial fluid for predicting early post-operative function and pain after fast-track total knee arthroplasty☆

Pawel Zietek [a], Violetta Dziedziejko [b], Krzysztof Safranow [b], Joanna Zietek [c], Marta Stępień-Słodkowska [d], Monika Bialecka [e], Maciej Zietek [f], Daniel Kotrych [a,*], Adam Kamiński [a], Aleksandra Kowalska [g]

[a] Department of Orthopaedics and Traumatology, Pomeranian Medical University, Szczecin, Poland
[b] Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Poland
[c] Zdroje Psychiatric Center, Szczecin, Poland
[d] Department of Physical Culture and Health Promotion, University of Szczecin, Szczecin, Poland
[e] Department of Experimental and Clinical Pharmacology, Pomeranian Medical University, Szczecin, Poland
[f] Department of Perinatology, Obstetrics and Gynecology, University of Szczecin, Szczecin, Poland
[g] Department of Stem Cells and Regenerative Medicine, Institute of Natural Fibres and Medicinal Plants, Poland

ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form 19 January 2016
Accepted 22 February 2016
Available online xxxx

Keywords:
TKA
Fast-track
Rehabilitation
Knee function
TNF-α

ABSTRACT

Background: Tumor necrosis factor-alpha (TNF-α) helps regulate neuroinflammation and anxiety and could conceivable predict early post-operative pain and function after fast-track total knee arthroplasty (TKA).
Methods: In patients with severe osteoarthritic knees undergoing TKA, we assessed: the correlations between pre-operative concentrations of TNF-α in synovial fluid; pre- and six-week post-operative knee function and pain; pre- and post-operative anxiety; pre- and post-operative synovial fluid concentrations of cartilage oligomeric matrix protein (COMP); age and body mass index (BMI).
Results: Of 100 enrolled patients, 78 had evaluable TNF-α data, and 58 had evaluable COMP data. Pre-operative TNF-α concentrations were inversely correlated with post-operative pain scores during walking ($r_S = -0.26$, $P = 0.03$) and with change of pain at rest during six weeks after TKA ($r_s = -0.28$, $P = 0.03$) and were directly correlated with a higher post-operative Knee Society score (KSS) ($r_S = 0.43$, $P < 0.001$) and with greater increases in this score during six weeks after TKA ($r_S = 0.33$, $P = 0.001$). Mean TNF-α concentrations were higher in the 39 patients reporting any pre-operative pain at rest than in 36 patients reporting no pre-operative pain ($P = 0.015$) and were the only independent predictor of pre-operative pain at rest (OR = 13, $P = 0.02$). Independent predictors of better post-operative knee function were higher log-transformed TNF-α concentrations ($\beta = 0.38$, $P = 0.002$) and male sex ($\beta = 0.28$, $P = 0.02$).
Conclusions: High levels of pre-operative TNF-α concentrations could be used as an independent predictor of better knee function at six weeks of follow-up. In patients with lower pre-operative TNF-α concentrations, post-operative pain management may improve the early outcome of the operated joint.

1. Introduction

Acute post-operative pain is a predictable, physiological response to tissue damage. However, major surgery can be especially physically and psychologically stressful for patients, and several environmental and genetic factors influence pain perception [1]. Pain mechanisms include the activation and release of local pro-inflammatory mediators, such as tumor necrosis factor α (TNF-α), accompanied by the destruction of tissue, a process mediated by proteases. Pain perception is also influenced by sex, race, ethnicity, social context, and interpretation of the pain experience [2–4].

In osteoarthritis (OA), pain perception is influenced by local factors and by the activation of central pain-processing pathways [5]. The polygenic nature of pain perception is also commonly known. Cartilage oligomeric matrix protein (COMP), an important degradation product of articular cartilage, is a potential predictor of knee OA, and its attendant pain [6]. However, few studies have prospectively related concentrations of COMP to knee pain and function in relation to the

☆ Ethical approval: The study was planned according to the statement of Human and Animal Rights. It has been approved by the local Bioethical Committee. Written informed consent was obtained from all patients. The study has been adhered to the tenets of the Declaration of Helsinki.

* Corresponding author at: Department of Orthopaedics, Traumatology and Orthopaedic Oncology, Pomeranian Medical University of Szczecin, Unii Lubelskiej 1 Street, 71-252 Szczecin, Poland. Tel.: +48 91 4253236; fax: +48 91 4253246.
E-mail address: dkotrych@iwnirz.pl (D. Kotrych).

http://dx.doi.org/10.1016/j.knee.2016.02.013
0968-0160/

development of knee OA and the outcomes of total knee arthroplasty (TKA) [7].

Pain after TKA is associated with TNF-α serum concentrations. Stannus et al. [8] found that baseline TNF-α was associated with change in pain while standing ($P = 0.033$). TNF-α concentrations are also important in immunity and in the normal, non-inflammatory physiological functioning of the central nervous system [9–11], learning and memory formation, and modulating states of depression, anxiety, [10,12,13], and emotional behavior, which may be related to alterations in serotonin metabolism [14].

We determined whether concentrations of TNF-α and COMP in synovial fluid were correlated with pre- or post-operative knee pain and function six weeks after TKA to evaluate their utility in predicting early post-operative outcomes. We also assessed the correlation between TNF-α concentrations and state- and trait-anxiety, and between TNF-α and COMP concentrations with age and body mass index (BMI) of patients with severe osteoarthritic knees undergoing fast-track TKA.

2. Patients and methods

2.1. Study design

The study was planned according to the statement of Human and Animal Rights. It was approved by the local Bioethical Committee of Pomeranian University Hospital. Written informed consent was obtained from all patients. The study adhered to the tenets of the Declaration of Helsinki.

Patients undergoing fast-track TKA in the department of Pomeranian University Hospital between 1 January and 30 April 2014 were eligible for the study if they were 18 to 80 years old, had Kellgren and Lawrence radiographic stage III or IV primary osteoarthrosis [15], an American Society of Anesthesiologists score of I to III, and were operated on by the same surgeon. Patients were excluded if they had rheumatoid arthritis, systemic or metabolic disorders, previous major surgery on the affected joint (e.g., arthrotomy, proximal tibial osteotomy, operated tibial plateau fracture), neurologic or psychiatric disease, or a history of alcohol abuse.

All patients received a cemented, total semi-constrained, posterior cruciate-substituting Triathlon prosthesis (Stryker, Kalamazoo, MI, USA) under standard anesthesia and analgesia, and underwent standard fast-track rehabilitation. The rehabilitation was started four to six hours post-operatively, just after recovery from spinal anesthesia. A rehabilitation protocol included intensive muscle strengthening, physical therapy exercises with active and passive range-of-motion (ROM) exercises, active isometric contractions of the quadriceps, exercises to improve activities of daily living (e.g., transition from sitting to standing), and walking with full-weight-bearing with a high rolling walker on the day of surgery, walking with crutches one day after surgery, and stair climbing two days after surgery. No continuous passive motion exercises or neuromuscular electrical stimulations (NMESs) were performed. However, on the day of surgery, cold compression bandages were applied for 10 min several times a day [16]. On the morning of surgery, all patients began receiving multimodal post-operative analgesia with oxycodone subcutaneously dosed by weight twice a day, oxycodone orally dosed by weight once a day, metamizol 4 × 1 g intravenously, and acetaminophen (paracetamol) on request. Tramadol and acetaminophen were to be continued after discharge.

2.2. Data collection

Sex, age, and BMI were recorded for all patients. Patients were evaluated for knee function and pain by the same surgeon pre-operatively and six weeks after surgery.

Knee score was assessed with the Knee Society score (KSS), which has questions to be answered by both patients and surgeons, and measures pain, stability, and ROM. Scores range from zero (worst) to 100 (best) [17]. A separate KSS for function reflects patient-reported walking distance and stair climbing and makes deductions for use of a walking aid, and also ranges from zero (worst) to 100 (best). On both scores, points are added or subtracted for various components.

Patients indicated the severity of knee pain on a 10-cm visual analog scale (VAS), anchored at no pain (zero) and worst pain imaginable [10] while supine and at rest and while walking [18]. The range of knee flexion and extension was measured with a standard goniometer with the patient supine.

Patients completed the Spielberger State-Trait Anxiety Inventory (STAI) questionnaire within eight hours of hospital admission for evaluating state anxiety (20 items) and trait anxiety (20 items) using a four-point scale (1, not at all/almost never; 2, somewhat/sometimes; 3, moderately so/often; 4, very much so/almost always). Scores ranged from 20 to 80 on each dimension, with higher scores indicating more anxiety [19].

2.3. Measurement of TNF-α and COMP concentrations in synovial fluid

Synovial fluid was collected from the knees using a syringe with a needle just before surgery. Samples were stored in tubes containing ethylenediaminetetraacetic acid (EDTA) and were frozen at 70 °C. Concentrations were measured for each patient using a commercial enzyme-linked immunosorbent assay (ELISA, Quantikine kits (R&D Systems, Minneapolis, MN, USA)), according to the manufacturer's protocol. High-sensitivity Quantikine kits were used to measure TNF-α concentrations (mean minimum detectable concentration 0.106 pg/ml, intra-assay precision CV% = 5.4%, inter-assay precision 8.3%) and Quantikine kits to measure COMP concentrations (mean minimum detectable concentration 0.010 ng/ml, intra-assay precision 3.2%, inter-assay precision 4.6%). Absorbance was read at 490 nm (for TNF-α) and 450 nm (for COMP) using an $EL_X\ 808_{IU}$ automated Microplate Reader (Bio-Tek Instruments Inc.). The results were analyzed using a log–log quadratic curve fit.

2.4. Statistical methods

Correlations between quantitative variables were assessed with Spearman's rank correlation coefficient (r_S) and subgroups were compared with Mann–Whitney tests. Post-operative changes of parameters were calculated as differences between the values measured six weeks before and after surgery. Independent predictors of pain and knee function after surgery were identified with multiple linear regression and logistic regression analyses including patients' age, sex and synovial fluid TNF-α as independent variables. Concentrations of TNF-α were successfully transformed logarithmically before inclusion into the multivariate models. Alpha was set at 0.05. Data were analyzed with the Statistica software program, Version 10.0 (StatSoft Inc., USA).

Our study had 80% statistical power to detect true correlations between biomarkers and clinical features with $r_S = 0.32$ for TNF-α ($n = 78$) and $r_S = 0.36$ for COMP ($n = 58$).

3. Results

Of the 100 consecutive patients who underwent fast-track rehabilitation after staged TKA during the study period, 22 were excluded: seven did not meet the inclusion criteria, 14 were excluded because synovial fluid was not properly sampled (blood-stained color of aspirates), and one was lost to follow-up. All included patients were assigned to TNF-α and COMP concentrations measurement. Of the included patients, TNF-α concentrations were available for 78 (48 women), and COMP concentrations were available for 58 (38 women; Table 1). The data are reported in the CONSORT flow diagram (Figure 1).

Pre-operative TNF-α concentrations were inversely correlated with post-operative pain while walking ($r_S = -0.26$, $P = 0.03$, Figure 2A) and with change of pain at rest during six weeks after operation ($r_S = -0.28$, $P = 0.03$). TNF-α correlated positively with KSS scores at six weeks after surgery ($r_S = 0.43$, $P < 0.001$, Figure 2B), and with post-operative change in this score during six weeks ($r_S = 0.33$, $P = 0.0097$, Figure 2C). Higher log-transformed TNF-α concentrations ($\beta = 0.38$, $P = 0.002$) and male sex ($\beta = 0.28$, $P = 0.02$) were the only factors tested that independently predicted higher post-operative KSS scores (Table 2).

Please cite this article as: Zietek P, et al, TNF-α concentrations in pre-operative synovial fluid for predicting early post-operative function and pain after fast-track total..., Knee (2016), http://dx.doi.org/10.1016/j.knee.2016.02.013